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14. Abstract

Prostate inflammation or infection may increase the risk of prostate cancer. As antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat prostatitis and urinary tract infections (UTIs), our objective was to assess whether their use decreases the risk of prostate cancer. We conducted a case-control study among men with incident prostate cancer (N=65 cases) and without prostate cancer (N=195 controls) at the San Francisco Veteran Affairs medical center (VAMC) between June 1996 and June 2006. Neither total antibiotic use nor total anti-inflammatory use reduces the risk of prostate cancer (P >0.05). Our analysis did not reveal a relation between use of antibiotics or NSAIDs and the risk of prostate cancer.

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INTRODUCTION

Prostate cancer is a major cause of morbidity and mortality in the United States and worldwide. Age, race, and family history are known risk factors for prostate cancer, but there is also limited biological and epidemiological evidence that suggest prostate inflammation or infection, also known as prostatitis, may increase the risk of prostate cancer [1-2]. Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are often used to treat prostatitis and urinary tract infections (UTIs) in men. Although prostatitis may be present in patients diagnosed with prostate cancer, the prevalence and incidence of prostatitis are thought to exceed that of prostate cancer [1-6].

Our hypothesis is that antibiotic use and/or use of NSAIDs may decrease the risk of prostate cancer. There is strong and consistent evidence from animal and laboratory studies, which suggest that regular use of NSAIDs may reduce prostate cancer risk [7-9]. Previous studies also indicate that NSAIDs have an inhibitory effect on prostate cancer cells, which suggests that prostaglandins play a pivotal role in prostate cancer biology [10-15]. Although cyclooxygenase-mediated production of prostaglandins appears to play an important role in the biology of prostate cancer, NSAIDs may have several mechanisms of action against prostate cancer, including apoptosis, inhibition of angiogenesis and cellular growth [16, 7-9].

Chemoprevention of prostate cancer, which is the primary focus of our study, evaluates drugs which may reduce the risk of prostate cancer with the goal of reducing the incidence of prostate cancer, as well as reducing treatment-related morbidity [17]. Our study examines whether known treatment for prostatitis, such as antibiotics and anti-inflammatory drugs, decreases the risk of subsequent prostate cancer. This is the first study to evaluate the effect of antibiotics on prostate cancer risk.

BODY

Statement of Work

Specific Aim 1

To describe the prevalence of symptoms of prostatitis; their distribution by race/ethnicity, age, socioeconomic status; and their association with urinary tract infections in the Boston Area Community Health survey (BACH).

Methods. A racially and ethnically diverse community-based survey of adults aged 30-79 years in Boston, Massachusetts. The BACH survey has recruited adults in three racial/ethnic groups: Latino, African American, and White using a stratified cluster sample. The target sample size is equally distributed by gender, race/ethnicity, and age. This report gives estimates on a sample of 2301 men: 700 African American, 766 Latino, and 835 White. Symptoms of chronic prostatitis were derived from the pain and urinary symptom domains of the NIH Chronic Prostatitis Symptom Index. A score of ≥10 (moderate-to-severe) on the Index was defined as symptoms suggesting prostatitis. A χ^2 statistic was computed to test the association of symptoms of prostatitis with categorical variables. Multiple logistic regression was used for the association of symptoms of prostatitis and multiple variables, and to calculate odds ratios and 95% confidence intervals (CIs).

Results. The overall prevalence of symptoms of prostatitis is 4.3%. In a multiple logistic regression model, the number of urinary tract infections, particularly ≥2, was associated with chronic prostatitis symptoms. Persons with a history of 2 infections had 3 times the odds, and with ≥3 infections had 7.6 times the odds, to have current symptoms of chronic prostatitis (*P*=.0006).

Conclusions. There is a strong association between current symptoms of chronic prostatitis and a history of urinary tract infections, particularly multiple infections. Further study is needed to determine whether prevention of recurrent infections can reduce the risk of chronic prostatitis.

***See published manuscript in Appendix.**

Statement of Work

Specific Aim 2

To assess the incidence of prostatitis with atypia and low-grade and high-grade prostatic intraepithelial neoplasia (LG-PIN/HG-PIN) and prostate cancer in men undergoing prostate biopsies in a prospective cohort study.

We conducted a case-cohort study within the Osteoporotic Fractures in Men Study (MrOS). MrOS is a community-based study of 5,995 men from six geographic regions of the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California. To be a MrOS participant, men had to be at least 65 years old, able to walk without the assistance of another person, not have had bilateral hip replacements, and have completed a minimum set of study measures (self-administered questionnaire, height, weight, bone density scan and vertebral radiograph). Participants were recruited from their communities, using population-based listings, such as motor vehicle registrations, targeted community presentations, and community and senior newspaper advertisements. Responses to mass mailings at some sites surpassed 10% to 15%,

and appointment show rates averaged above 85%, reflecting a high interest and commitment to this study.

Prostate Cancer Adjudication. Prostate cancer cases were identified through self-report using a mailed triannual follow-up questionnaire. For study participants who did not return the questionnaire, information about prostate cancer diagnosis was elicited through in-person or telephone interviews. For each prostate cancer report, medical records were requested from the hospital or clinic including the following: pathology reports, Prostate Specific Antigen (PSA) laboratory reports, clinical notes, reason for prostate biopsy, staging studies, and treatment notes. All medical records were reviewed and prostate cancer diagnosis adjudicated centrally at the MrOS coordinating center (University of California, San Francisco). We randomly reviewed 446 prostate pathology reports to assess pathological findings and associations.

Results

Summary statistics of those with and without prostate cancer in MrOS

	Prostate Cancer		
	No (n=259)	Yes (n=187)	
	N(%)	N(%)	p-values
	Mean ± SD	Mean ± SD	
Age	70.1 ± 3.8	72.5 ± 5.3	<.0001
UAU-SS	9.3 ± 6.0	8.1 ± 6.3	0.05
PSA level	11.0 ± 9.0	11.6 ± 16.3	0.46
# of cores taken on biopsy	11.5 ± 3.9	11.2 ± 4.1	0.39
Gleason sum	6.7 ± 0.8	6.7 ± 1.0	0.99
Acute prostatitis			
No	70 (66.7)	24 (70.6)	0.94
Yes	30 (28.6)	9 (26.5)	
Uncertain	5 (4.8)	1 (2.9)	
ASAP noted on report	19 (7.3)	19 (10.2)	0.29
Atypia/PIN mixture noted	3 (1.2)	1 (1.1)	0.93
Chronic prostatitis			
No	9 (8.6)	1 (2.9)	0.63
Yes	91 (86.7)	32 (94.1)	
Uncertain	5 (4.8)	1 (2.9)	
# of cores taken uncertain	73 (28.2)	35 (18.7)	0.02

HG-PIN			
No	3 (7.3)	2 (4.1)	0.43
Yes	35 (85.4)	46 (93.9)	
Uncertain	3 (7.3)	1 (2.0)	
Hyperplasia noted	58 (22.4)	21 (11.2)	0.002
LG-PIN			
No	35 (85.4)	45 (91.8)	0.53
Yes	3 (7.3)	3 (6.1)	
Uncertain	3 (7.3)	1 (2.0)	
PIN noted on report	41 (15.8)	49 (26.2)	0.007
Prostatitis noted on report	105 (40.5)	34 (18.2)	<.0001
Site			
Birmingham	71 (68.9)	32 (31.1)	0.009
Minneapolis	92 (60.1)	61 (39.9)	
Palo Alto	52 (46.4)	60 (53.6)	
Pittsburgh	44 (56.4)	34 (43.6)	
Caucasian	226 (87.3)	170 (90.9)	0.23
Alpha-andrenergic blockers	59 (24.3)	37 (21.3)	0.47
Cox II inhibitors	15 (6.2)	18 (10.3)	0.12
NSAIDS*	41 (16.9)	30 (17.2)	0.92
Antiandrogen use	0	0	
Androgen use	3 (1.2)	2 (1.2)	0.99
Smoke			
Never	101 (39.0)	82 (43.9)	0.56
Past	149 (57.5)	100 (53.5)	
Current	9 (3.5)	5 (2.7)	
Obesity (BMI 30+)	61 (23.6)	41 (21.9)	0.69
Family hx of prostate cancer	40 (18.7)	38 (23.6)	0.25
Ever had prostatitis	74 (28.6)	52 (27.8)	0.86
Tumor stage			
N0	15 (50.0)	80 (44.2)	0.81
N1	0 (0.0)	3 (1.7)	
NX	15 (50.0)	98 (54.1)	

*prescription only

Conclusion

Prostatitis on prostate biopsies was not correlated with atypia, LG-PIN, HG-PIN or prostate cancer.

Statement of Work

Specific Aim 3

Prostate inflammation or infection may increase the risk of prostate cancer. As antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat prostatitis and urinary tract infections (UTIs), our objective was to assess whether their use decreases the risk of prostate cancer.

METHODS: We conducted a case-control study among men with incident prostate cancer (N=65 cases) and without prostate cancer (N=195 controls) at the San Francisco Veteran Affairs medical center (VAMC) between June 1996 and June 2006. Cases were all patients who had prostate biopsies positive for cancer. We matched controls to cases on age group and race at a 3:1 ratio, and each matched pair was given an identical index date. Total antibiotic and NSAID use (number of prescriptions) was computed for each participant by drug type and was restricted to a fill date at least 1 year before the index date. Logistic regression was used for analysis. We adjusted for the matching variables (age group and race) and potential confounders (years of VAMC enrollment and number of clinic visits).

RESULTS: Neither total antibiotic use nor total anti-inflammatory use reduces the risk of prostate cancer (P >0.05).

CONCLUSIONS: Our analysis did not reveal a relation between use of antibiotics or NSAIDs and the risk of prostate cancer.

To investigate our hypothesis that antibiotics and NSAIDs (refers only to non-aspirin, nonselective NSAIDs) decrease the risk of incident prostate cancer, we conducted a case-control

study of patients diagnosed with prostate cancer and compared them to general internal medicine clinic-based controls without known prostate cancer, frequency-matched to cases on age and race/ethnicity. Our study design is similar to studies performed evaluating the association between antibiotics and breast cancer [18-20].

We used computerized medical record information from the San Francisco VAMC. Patients eligible for the study were men enrolled at SF Veterans Administration Medical Center (VAMC) system before July 1, 2000 and were at least 40 years of age or older at the time of VAMC enrollment. In addition, patients had to have at least one prostate specific antigen (PSA) test in the past 10 years (between June 1996 and June 2006) and must have been seen in a General Medicine Practice Clinic on two or more occasions between June 1996 and June 2006. The study protocol was approved by the Committee on Human Research of the University of California, San Francisco. Variables extracted included race and ethnicity, prostate biopsy results, prostate cancer diagnosis, history of acute or chronic prostatitis; number of health care visits, history of UTIs (clinically diagnosed or urine testing with white blood cell count of >10), history of benign prostatic hyperplasia (BPH). The pharmacy database was used to determine the amount and duration of antimicrobial and non-steroidal anti-inflammatory use (including the cumulative number of days of medication use and the total number of prescriptions) for the following medications: antibiotics (macrolides, azithromycin, erythromycin, clarithromycin, tetracyclines, doxycycline, penicillins, cephelexin, cephalosporins, sulfonamides, TMP-SMX, ciprofloxacin, levofloxacin), antivirals, antifungals, anti-inflammatory medications (non-steroidal anti-inflammatory medication, COX-2 inhibitors, aspirin, anti-TNF medications), and other medications of interest (testosterone, finasteride, alpha receptor blockers).

We identified 65 patients with a recorded biopsy-positive prostate cancer. We conducted a case-control study among men with incident prostate cancer (N=65 cases) and without prostate cancer (N=195 controls) at the SF VAMC between June 1996 and June 2006. Cases were all patients who had prostate biopsies positive for cancer. The prostate cancer diagnosis date was designated as the index date. We randomly matched controls to cases on age group and race at a 3:1 ratio, and each matched pair was given an identical index date. Total antibiotic (anti-bacterial agents only), antimicrobial use (antibacterial, antivirals, and antifungals combined) and NSAIDs, or aspirin use (number of prescriptions) was computed for each participant by drug type and was restricted to a fill date at least 1 year before the index date. Logistic regression was used for analysis. We adjusted for the matching variables (age group and race, which are well-accepted risk factors for prostate cancer) as well as for potential confounders (years of VAMC enrollment and number of clinic visits) which increase the likelihood of having a prostate cancer diagnosis. We used STATA 9.2 (STATCORP, College Station, TX) for statistical analysis. A multiple logistic regression model was used to model the overall association of antibiotics, antimicrobials, NSAIDs, aspirin use and multiple covariates and was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). Quantity of medication use was grouped into five categories according to increasing number of prescriptions prescribed.

Demographic and some health characteristics for the VA sample are reported in Table 1 (see supporting materials). In our analysis, 65 case-patients and 195 control-patients were included in our analysis. Median age of case-patients was 78 years (range: 51-99 years) vs. 77 years

(range: 52-96 years) for control-patients. The majority of study participants were White (43%) or Black (26%). Although not statistically significant, case-patients (87%) were more likely than control-patients (77%), to have a history of UTI (*P*=.08). Case-patients had a greater number of clinic visits (mean 146) compared to control-patients (mean 123) *P*=0.01. There were 14 (7%) control-patients who had finasteride use, with an average of 398.6 doses per individual. None of the prostate cancer patients had prior finasteride use.

In a multiple logistic regression model (Table 2, see supporting materials), after adjustment for the matching variables (age group and race), as well as the potential confounders (number of UTIs, years of enrollment, and number of visits), total antibiotic use, antimicrobial use, anti-inflammatory use, or aspirin use did not reduce the risk of incident prostate cancer. A higher levels of antibiotic, nsaid, and aspirin use was also not associated with a reduced risk of prostate cancer (tests for trend, p= 0.33, 0.23, and 0.35, respectively). Subgroup analysis for specific classes of antibiotics (cephalosporins, macrolides, penicillins, quinolones, sulfonamides, and tetracyclines) also did not reveal any significant effect on prostate cancer risk (data not shown).

Our analysis did not reveal an association between the use of antibiotics, NSAIDs, or aspirin and the risk of prostate cancer; however, the width of the confidence intervals does not rule out a protective effect. Our study is the first report to assess the relationship between prostate cancer and antibiotics. It is plausible that some classes of antibiotics may have an effect on prostate cancer by reducing prostate infections and inflammatory responses. Both microbiological and epidemiologic studies show that microbes that commonly infect or inflame the prostate may be

associated with prostate cancer [21-28]. To further clarify whether antimicrobial agents influence prostate cancer, studies in a larger sample, given our wide confidence intervals, should be strongly considered to definitively answer this research question. For example, the confidence interval examining the effect of antibiotics (0.30 to 1.98) includes a potential 70% reduction in the odds of prostate cancer among the highest users of antibiotics. Studies with a larger number of patients will be able to more precisely estimate the true effect of these medications.

Previous epidemiological studies have assessed the association of NSAIDs with prostate cancer. Studies have found that NSAIDs or aspirin may reduce the risk of prostate cancer; differences have been found between NSAIDs and aspirin use and prostate cancer risk [10-13], so our evaluation also analyzed these classes of medications separately. In a cross-sectional, self-administered survey of over 1200 Canadian men, aspirin use was associated with a 42% reduction in the odds of prostate cancer, but NSAIDs were not related to prostate cancer risk [12]. In a longitudinal study of predominantly white men in Minnesota (n=1362), age 50-79 years, NSAIDs use had a relative odds of 0.45 (95% CI 0.28-0.73) with 6 years of follow-up [13]. Unfortunately, this study only assessed NSAIDs use at baseline [13]. In a case-control study of men age 65 years and older who had undergone prostate biopsy, NSAIDs/COX-2 inhibitors or aspirin use during a 2 year period reduced the likelihood of prostate cancer with over 2000 cases and similar number control participants with NSAIDs/COX-2 inhibitors: OR 0.71 (95% CI 058-0.86) and aspirin: OR 0.84 (95% CI 0.74-0.96) [11]. A systematic review of 12 studies (5 retrospective and 7 prospective) found a summary odds ratio for aspirin and prostate cancer risk of 0.9 (95% CI 0.82-0.99), but reduction in risk with the use of other

NSAIDs was less consistent with a combined OR 0.87 (95% CI 0.61-1.23) [10]. Despite substantial evidence of a reduced incidence of prostate cancer with NSAIDs or aspirin use, neither medication is currently prescribed as a primary chemopreventative measure for prostate cancer, given potential medication side effects and the lack of data from a randomized controlled trial.

Potential limitations of our study should be recognized. We limited our analysis to the number of pills prescribed to patients and filled by patients. It is unknown whether patients actually took the medications that were prescribed once their prescriptions were filled. Thus, the exposure measure may have incorrectly categorized patients according to the number of medication exposures. Future studies assessing the relationship between antibiotic use and prostate cancer risk should consider including only men who are at particularly high risk for prostate cancer, such as those with high-grade prostatic intraepithelial neoplasia **(**HG-PIN) on prostate biopsies (a known precursor of prostate cancer) or those with strong family histories or African American race, instead of selecting all men which may mitigate detection of true effect. Limiting the selection of patients to those who have undergone a prostate biopsy may also reduce, but not eliminate, the possibility of detection bias.

In summary, current data from the San Francisco VAMC database does not provide evidence of support for the hypothesis that antibiotics or NSAIDs decrease the risk of prostate cancer.

Statement of Work

Specific Aim 4

Although sex steroids have been implicated in the pathogenesis of prostate cancer, epidemiologic studies have been inconsistent on whether circulating sex hormones are associated with prostate cancer risk. Goal of our study was to assess baseline hormones levels and incident prostate cancer

Methods: A case-cohort study was conducted within the ongoing Osteoporotic Fractures in Men (MrOS) cohort study of community-dwelling men ≥65 years old recruited at 6 US clinical sites. All incident prostate cancer cases occurring from March 2000 through July 2006 were included in the study. Men with a history of prostate cancer prior to baseline and those who reported androgen or antiandrogen therapy at baseline were excluded. The resulting analytic sample comprised 275 cases and 1652 non-cases with complete sex hormone measurements. Subjects completed questionnaires about demographic, clinical and lifestyle factors and submitted serum samples for analysis of testosterone, estradiol, and sex hormone-binding globulin (SHBG). Sex hormones were assayed by gas chromatograph/mass spectrometry, and free and bioavailable testosterone and estradiol were calculated. Associations between time to incident prostate cancer and each sex hormone were evaluated using Cox proportional hazards regression models adjusted for age, race, study site, and weight. Hazard ratios (HR) and 95% confidence intervals (CI) were examined per standard deviation (SD) change and by quartile of each sex hormone.
Results: In the case-cohort, the mean age was 73 years, mean total testosterone was 411 ng/dl; mean bioavailable testosterone was 207 ng/dl; mean free testosterone was 7.9 ng/dl; mean estradiol was 23 ng/dl; and mean SHBG was 49.4 nM. Compared to men without prostate cancer, hormone values did not differ ($p>0.05$ for all comparisons). The adjusted HR per SD increase in free testosterone was 1.07 (CI 0.94-1.21), and was 1.11 (CI 0.97-1.28) per SD decrease in SHBG. The adjusted HR per SD increase in free estradiol was 1.09 (CI 0.96-1.23).
Conclusions: In this cohort of older men, sex hormone levels at baseline were not significantly associated with incident prostate cancer.

KEY RESEARCH ACCOMPLISHMENTS

Statement of Work #1

- The overall prevalence of symptoms of prostatitis is 4.3%. Persons with a history of 2 infections had 3 times the odds, and with ≥3 infections had 7.6 times the odds, to have current symptoms of chronic prostatitis (*P*=.0006).

Statement of Work #2

- High-grade prostatic intraepithelial neoplasia and prostatitis on prostate biopsies were not correlated with the presence of prostate cancer on biopsies.

Statement of Work #3

- Neither total antibiotic use nor total anti-inflammatory use reduces the risk of prostate cancer ($P > 0.05$).

Statement of Work #4

- Compared to men without prostate cancer, sex hormone values did not differ ($p > 0.05$ for all comparisons) in prostate cancer patients.

REPORTABLE OUTCOMES

Manuscripts/Publications

1. **Daniels NA,** Ewing SK, Zmuda JM, Wilt TJ, Bauer DC for the Osteoporotic Fractures in Men (MrOS) Research Group. Prevalence and Correlates of Prostatitis in a large community-based cohort of older men. *Urology* 2005;66:964-70.
2. **Daniels NA,** Link CL, Barry MJ, McKinlay JB for the BACH Survey Investigators. Are Past Urinary Tract Infections Associated with Current Symptoms of Chronic Prostatitis/Chronic Pelvic Pain Syndrome: Results from the Boston Area Community Health (BACH) Survey. *Journal of the National Medical Association* May 2007;99:509-516.
3. **Daniels NA, Chen YH, Bent S.** Antibiotic and Anti-Inflammatory Use and the Risk of Prostate Cancer: A Pilot Study. BMC Research Notes 2009 (In Press)

Abstracts

Nicholas A. Daniels*, University of California, San Francisco; Carrie M. Nielson, Oregon Health & Science University; Andrew R. Hoffman, Stanford University; Douglas C. Bauer, University of California, San Francisco for the Osteoporotic Fractures in Men (MrOS) Study Group. SEX HORMONES AND PROSTATE CANCER RISK. American Urological Association Annual Meeting, Chicago, Illinois, April 26, 2009 (Accepted for Podium Presentation)

Daniels NA, et al**.** Association Between Past Urinary Tract Infections and Current Symptoms Suggestive of Chronic Prostatitis/Chronic Pelvic Pain Syndrome. Prostate Cancer Research Program Meeting, Innovative Minds in Prostate Cancer Today (IMPaCT), Department of Defense, Atlanta, Georgia, September 7, 2007.

Daniels NA, et al**.** Are Urinary Tract Infections Associated with Prostatitis Symptoms: Results from the Boston Area Community Health (BACH) Survey. American Urological Association Annual Meeting, Moderated Poster Presentation, May 2005, San Antonio, TX.

Daniels NA, Ewing SK, Zmuda JM, Wilt TJ, Bauer DC**.** Prevalence and Correlates of Prostatitis in a large community-based cohort of older men. American Urological Association Annual Meeting Oral Presentation, May 2004, San Francisco, CA.

CONCLUSIONS

SOW 1

There is a strong association between current symptoms of chronic prostatitis and a history of urinary tract infections, particularly multiple infections. Further study is needed to determine whether prevention of recurrent infections can reduce the risk of chronic prostatitis.

SOW 2

High-grade prostatic intraepithelial neoplasia and prostatitis on prostate biopsies were not correlated with the presence of prostate cancer on biopsy. Further study is needed to determine whether chronic prostatitis on prostate biopsies is correlated with finding prostate cancer.

SOW 3

Our analysis did not reveal a relation between use of antibiotics or NSAIDs and the risk of prostate cancer. A larger study using the entire VA system database (not only the San Francisco VA system database) would provide additional power to detect a relationship between antibiotics or NSAIDs and the risk of prostate cancer.

SOW 4

In this cohort of older men, sex hormone levels at baseline were not significantly associated with incident prostate cancer. Serials measurement of sex hormones of the course of a man's lifetime may be required to better assess sex hormones levels and incident prostate cancer.

REFERENCES

1. Roberts RO, Bergstralh EJ, Bass SE, Lieber MM, Jacobsen SJ. Prostatitis as a risk factor for prostate cancer. *Epidemiology* 2004:**15**:93-9

2. Dennis LK, Lynch CF, Torner JC. Epidemiologic association between prostatitis and prostate cancer. *Urology* 2002:**60**:78-83

3. Roberts RO, Jacobson DJ, Girman CJ, Rhodes T, Lieber MM, Jacobsen SJ. Prevalence of prostate-like symptoms in a community based cohort of older men. *J Urology* 2002:**168**:2467-2471

4. McNaughton M, Meigs JB, Barry MJ, Walker Corkey E, Giovannucci E, Kwachi I. Prevalence and correlates of prostatitis in the health professionals follow-up study cohort. *J Urology* 2002:**167**:1363-1366

5. Weidner W, Schiefer HG, Krauss H, Jantos C, Friedrich HJ, Altmannsberger M. Chronic prostatitis: a thorough search for etiologically involved microorganisms in 1,461 patients. *Infection* 1991:**19** Suppl 3:S119-25

6. Collins MM, Stafford RS, O'Leary MP, Barry MJ. How common is prostatitis? A National Survey of Physician Visits. *J Urology* 1998:**159**:1224-1228

7. Kirschenbaum A, Liu X, Yao S, Levine AC. The role of cyclooxygenase-2 in prostate cancer. *Urology* 2001:**58**:127-31

8. Kirschenbaum A, Klausner AP, Lee R, Unger P, Yao S, Liu XH, Levine AC. Expression of cyclooxygenase-1 and cyclooxygenase-2 in the human prostate. *Urology* 2000:**56**:671-6

9. Liu XH, Kirschenbaum A, Yao S, Lee R, Holland JF, Levine AC. Inhibition of cyclooxygenase-2 suppresses angiogenesis and the growth of prostate cancer in vivo. *J Urol* 2000:**164**:820-5

10. Mahmud S, Franco E, Aprikian A. Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis. *Br J Cancer* 2004:**90**:93-9

11. Dasgupta K, Di Cesar D, Ghosn J, Rajan R, Mahmud S, Rahme E. Association between nonsteroidal anti-inflammatory drugs and prostate cancer occurrence. *Cancer J* 2006:**12**:130-5

12. Mahmud SM, Tanguay S, Begin LR, Franco EL, Aprikian AG. Non-steroidal anti-inflammatory drug use and prostate cancer in a high-risk population. *Eur J Cancer Prev* 2006 :**15**:158-64

13. Roberts RO, Jacobson DJ, Girman CJ, Rhodes T, Lieber MM, Jacobsen SJ. A population-based study of daily nonsteroidal anti-inflammatory drug use and prostate cancer. *Mayo Clin Proc* 2002:**77**:219-25

14. Rotem R, Tzivony Y, Flescher E. Contrasting effects of aspirin on prostate cancer cells: suppression of proliferation and induction of drug resistance. *Prostate* 2000:**42**:172-80

15. Hsu AL, Ching TT, Wang DS, Song X, Rangnekar VM, Chen CS. The cyclooxygenase-2 inhibitor celecoxib induces apoptosis by blocking Akt activation in human prostate cancer cells independently of Bcl-2. *J Biol Chem* 2000:**275**:11397-403

16. Myers C, Koki A, Pamukcu R, Wechter W, Padley RJ. Proapoptotic anti-inflammatory drugs. *Urology* 2001:**57**(4 Suppl 1):73-6

17. Sporn MB, Suh N. Chemoprevention: an essential approach to controlling cancer.
Nat Rev Cancer 2002:**2**:537-43

18. Garcia Rodriguez LA, Gonzalez-Perez A. Use of antibiotics and risk of breast cancer. *Am J Epidemiol* 2005:**161**:616-9

19. Kaye JA, Jick H. Antibiotics and the risk of breast cancer. *Epidemiology* 2005:16:688-90

20. Velicer CM, Heckbert SR, Lampe JW, Potter JD, Robertson CA, Taplin SH. Antibiotic use in relation to the risk of breast cancer. *JAMA* 2004:**291**:827-35

21. Dennis LK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. *Epidemiology* 2002:**13**:72-79

22. Mandel JS, Schuman LM. Sexual factors and prostatic cancer: results from a case-control study. *J Gerontol* 1987:**42**:259-64

23. Pienta KJ, Esper PS. Risk factors for prostate cancer. *Ann Intern Med* 1993:**118**:793-803

24. Key T. Risk factors for prostate cancer. *Cancer Surv* 1995:**23**:63-77

25. Hayes RB, Pottern LM, Strickler H, Rabkin C, Pope V, Swanson GM, Greenberg RS, Schoenberg JB, Liff J, Schwartz AG, Hoover RN, Fraumeni JF Jr. Sexual behavior, STDs and risks for prostate cancer. *Brit J Cancer* 2000:**82**:718-725

26. Rosenblatt KA, Wicklund KG, Stanford JL. Sexual factors and the risk of prostate cancer. *Amer J Epidemiol* 2000:**153**:1151-1158

27. Fowler JE Jr. Antimicrobial therapy for bacterial and nonbacterial prostatitis. *Urology* 2002:**60**(6 Suppl):24-6

28. Krieger JN, Riley DE, Vesella RL, Miner DC, Ross SO, Lange PH. Bacterial DNA sequences in prostate tissue from patients with prostate cancer and chronic prostatitis. *J Urology* 2000:**164**:1221-1228

APPENDICES

ELSEVIER

CORRELATES AND PREVALENCE OF PROSTATITIS IN A LARGE COMMUNITY-BASED COHORT OF OLDER MEN

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ABSTRACT

Objectives. To describe the prevalence and correlates of self-reported history of prostatitis in terms of lower urinary tract symptoms and associated dissatisfaction in community-dwelling older men.

Methods. We performed a cross-sectional analysis from a prospective cohort study of 5821 men aged 65 years and older recruited from six clinical centers.

Results. Overall, 1439 men (25%) self-reported a history of prostatitis. Men with a history of prostatitis were more likely to self-report a history of prostate cancer (26% versus 7%; $P < 0.0001$) and a history of benign prostatic hyperplasia (83% versus 38%; $P < 0.0001$) within a lifetime compared with men without a history of prostatitis. Men with a history of prostatitis also had a greater mean American Urological Association symptom score (mean ± SD, 10.1 ± 7.1 versus 7.7 ± 5.9; $P < 0.0001$) than men without a history of prostatitis. Also, a greater percentage of men with a history of prostatitis reported being dissatisfied with their present urinary condition than did men without a history of prostatitis (21% versus 11%; $P < 0.0001$). We found positive associations for a history of prostatitis with a history of benign prostatic hyperplasia (odds ratio 8.0, 95% confidence interval 6.8 to 9.5), a history of prostate cancer (odds ratio 5.4, 95% confidence interval 4.4 to 6.6), and dissatisfaction with current urinary condition (odds ratio 1.2, 95% confidence interval 1.01 to 1.5).

Conclusions. A self-reported history of prostatitis is common in older men and was associated with self-reported prostate cancer and benign prostatic hyperplasia and increased severity of lower urinary tract symptoms and associated dissatisfaction. Because of the potential detection bias, recall bias, and the cross-sectional nature of the study, limiting causal inference, the associations among these urologic conditions require additional study. UROLOGY **66:** 964–970, 2005.

Prostate cancer is the most commonly diagnosed cancer among men in the United States, but the relationship between prostatitis and benign prostatic hyperplasia (BPH) and prostate cancer remains unclear. Limited epidemiologic evidence supports the hypothesis that prostatitis may be a risk factor for the development of prostate cancer.[1,2] The overall prevalence of prostatitis in North America is estimated at between 2% and 16%.[3–7]

Few studies have examined a prior history of prostatitis and urinary health correlates in older men. The objective of this study was to describe the

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This study was presented in part at the Annual Meeting of the American Urological Association, San Francisco, May 8–13, 2004 (podium session presentation).

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prevalence and correlates of a self-reported history of prostatitis in terms of current lower urinary tract symptoms (LUTS) and associated dissatisfaction and to examine the associations between prostatitis and BPH and prostate cancer in a cohort of community-dwelling older men who participated in the Osteoporotic Fractures in Men (MrOS) study.

MATERIAL AND METHODS

We conducted a cross-sectional analysis of baseline data from a prospective cohort study of 5821 men enrolled in the MrOS study. We excluded 174 men who were not white, African American, or Asian, because the number of men in other categories were too few for stratified analyses. The MrOS study is a community-based study of 5995 men from six clinical centers in the United States. To be an MrOS participant, men had to be at least 65 years old, able to walk without the assistance of another person, not have undergone bilateral hip replacements, and have completed a minimal set of study measures (self-administered questionnaire, height, weight, bone density scan, and vertebral radiography). Participants were recruited from their communities, using population-based listings, such as motor vehicle registrations, targeted community presentations, and community and senior newspaper advertisements. Responses to mass mailings at some sites surpassed 10% to 15%, and the appointment show rates averaged greater than 85%, reflecting the high interest and commitment to this study.

In the baseline questionnaire, participants were asked: "Has a doctor or other healthcare provider ever told you that you had or have prostatitis (inflammation or infection of the prostate)?" Our case definition for prostatitis was broad to capture patients diagnosed with either acute or chronic bacterial prostatitis or with chronic abacterial prostatitis. Participants were also asked: "Has your doctor or other healthcare provider ever told you that you have or had an enlarged prostate, also known as benign prostatic hyperplasia (BPH)? This means an enlarged prostate that is not due to cancer." Participants were also asked about a past history of prostate cancer.

Subjects completed questionnaires about demographic, clinical, and lifestyle factors; the American Urological Association (AUA) Symptom Score survey; and the supplemental International Prostate Symptom Score survey question. The AUA survey asked about lower urinary tract symptom frequency during the previous month.[8] Participants answered the supplemental International Prostate Symptom Score survey question about how they would feel if they were to spend the rest of their life with their current urinary condition. Possible responses included delighted, pleased, mostly satisfied, mixed (about equally satisfied and dissatisfied), mostly unsatisfied, unhappy, or terrible. Dissatisfaction with the present urinary condition was defined as answers of mostly unsatisfied, unhappy, or terrible. Questionnaire variables gathered at the baseline visit included demographics; medication use (any prescription medications taken daily or almost daily for at least the past month), prostate-specific medications, herbal remedies or supplements (currently taking daily or almost daily), and dietary information collected using a modified Block Food Frequency Questionnaire (Block Dietary Data Systems, Berkeley, Calif); and lifestyle factors. The Physical Activity Scale for the Elderly score was used to evaluate physical activity.

The baseline characteristics in men with and without a self-reported history of prostatitis (not categorized further) were compared using chi-square tests for homogeneity for categorical variables and *t* tests or Wilcoxon rank sum tests for continuous variables. We used multivariate logistic regression models to determine the independent correlates for a history of prostatitis. The multivariate models included variables with $P \leq 0.10$ in age-adjusted and BPH-adjusted logistic regression models. In addition, we ran forward, backward, and stepwise variable selection models, considering variables with $P \leq 0.10$ in the age-adjusted and BPH-adjusted models. We report here the odds ratios (ORs). We tested for interactions between the baseline characteristics and race, BPH, and prostate cancer. All statistical analyses were performed with Statistical Analysis Systems software, version 8.2 (SAS Institute, Cary, NC).

RESULTS

Overall, 1439 men (25%) reported a history of prostatitis. The racial prevalence distribution of prostatitis was 25% for white men, 23% for African-American men, and 17% for Asian men ($P = 0.02$). The prevalence of prostatitis by age category was 19% for those younger than 70 years, 25% for those 70 to 79 years, and 33% for those 80 years or older ($P < 0.0001$).

The baseline characteristics of men with and without a history of prostatitis are compared in Table I. Men with a history of prostatitis were older and a greater percentage was from the Birmingham site compared with men without a history of prostatitis. No association was found between a history of prostatitis and education, marital status, or body mass index. Men with a history of prostatitis more frequently reported poorer health and more often had comorbid conditions than did those without a history of prostatitis.

Men with a history of prostatitis were more likely to report a history of prostate cancer and a history of BPH than were men without a history of prostatitis. These men also had a greater mean AUA symptom score, and a greater percentage reported dissatisfaction with their present urinary condition compared with men without a history of prostatitis.

Compared with white men with a history of prostatitis, African-American men with a history of prostatitis had a greater mean AUA symptom score (12.6 ± 9.1 versus 10.1 ± 6.9; $P = 0.04$), and a greater percentage reported being mostly unsatisfied with their urinary condition (36% versus 21%; $P = 0.006$). Controlling for BPH and age did not alter these results (data not shown).

Multivariate logistic model results are presented in Table II. The model included variables that were associated with history of prostatitis at $P \leq 0.10$ in age-adjusted and BPH-adjusted logistic regression models. The OR estimates obtained from these models and from the final multivariate model were similar, although the strength of the associations (Table II) lessened after adjustment for other correlates in the model. After controlling for other covariates in the model, the odds of a prostatitis history increased by 8% per 5-year increase in age, more than fivefold for men with a history of prostate cancer, eightfold for men with a history of

TABLE I. *Comparison of baseline characteristics in men with and without a history of prostatitis*

Characteristic	Men with Prostatitis History (n = 1439)	Men Without Prostatitis History (n = 4382)	*P* Value
Demographics			
Age (yr)	75.0 ± 6.0	73.3 ± 5.8	<0.0001
Race			0.02
White	1352 (94)	4033 (92)	
African American	55 (4)	189 (4)	
Asian	32 (2)	160 (4)	
Education (yr)			0.85
<12	93 (6)	277 (6)	
≥12	1346 (94)	4105 (94)	
Marital status			0.30
Married	1174 (82)	3615 (83)	
Widowed	148 (10)	378 (9)	
Separated	12 (1)	35 (1)	
Divorced	66 (5)	238 (5)	
Never married	39 (3)	116 (3)	
Socioeconomic status (1–10 scale)			
Standing within community	6.8 ± 1.8	6.9 ± 1.7	0.04
Standing within United States	7.2 ± 1.8	7.2 ± 1.7	0.19
Site			0.003
Birmingham	280 (19)	680 (15)	
Minneapolis	228 (16)	763 (17)	
Palo Alto	202 (14)	713 (16)	
Pittsburgh	229 (16)	772 (18)	
Portland	256 (18)	727 (17)	
San Diego	244 (17)	727 (17)	
Medical history			
Current health status			<0.0001
Excellent/good	1174 (82)	3813 (87)	
Fair/poor/very poor	265 (18)	567 (13)	
Comorbidities (of 13 conditions)* (n)			<0.0001
None	129 (9)	751 (17)	
1 condition	346 (24)	1300 (30)	
2 conditions	391 (27)	1118 (25)	
3 conditions	280 (19)	696 (16)	
≥4 conditions	293 (20)	517 (12)	
Body mass index (kg/m^2)	27.4 ± 3.8	27.4 ± 3.9	0.97
Prostate health			
History of prostate cancer	375 (26)	320 (7)	<0.0001
History of BPH	1199 (83)	1646 (38)	<0.0001
AUA prostate symptom score (0–35 scale)	10.1 ± 7.1	7.7 ± 5.9	<0.0001
Dissatisfied with current urinary condition	307 (21)	480 (11)	<0.0001
Lifestyle			
Alcohol consumption			
Any alcohol in past year	888 (62)	2863 (65)	0.01
Drinks/wk (n)	3.9 ± 6.1	4.4 ± 7.0	0.09
Smoking (pack-years)	28.2 ± 24.9	29.3 ± 25.9	0.25
Caffeine intake (mg/day)	204 ± 229	218 ± 235	0.05
Physical activity			
Walks for exercise daily	721 (50)	2174 (50)	0.75
Physical Activity Scale for the Elderly (PASE) score	143 ± 68	147 ± 68	0.03
Medication use and dietary information			
Finasteride	93 (6)	85 (2)	<0.0001
Saw palmetto	211 (15)	415 (9)	<0.0001
NSAIDS	113 (8)	322 (7)	0.53
Alpha-blockers	351 (24)	526 (12)	<0.0001
Selenium intake from supplements (μg/day)	31.0 ± 59.9	25.2 ± 51.3	0.04
Vitamin E intake (a-TE/day)			

TABLE I. (continued).

Characteristic	Men with Prostatitis History (n = 1439)	Men Without Prostatitis History (n = 4382)	*P* Value
From food	9.6 ± 5.6	9.4 ± 6.1	0.04
From supplements	185.0 ± 202.0	170.3 ± 202.1	0.002
Total	194.6 ± 202.6	179.7 ± 202.7	0.0008
Calcium intake (mg/day)			
From food	812.2 ± 380.3	797.1 ± 390.3	0.20
From supplements	359.3 ± 436.3	335.1 ± 431.3	0.02
Total	1171.5 ± 575.2	1132.2 ± 595.1	0.03
Vitamin D intake (IU/day)			
From food	170.2 ± 117.5	163.9 ± 117.9	0.03
From supplements	232.9 ± 209.1	225.9 ± 208.6	0.25
Total	403.1 ± 245.9	389.8 ± 245.3	0.08

KEY: BPH = benign prostatic hyperplasia; AUA = American Urological Association; NSAIDS = nonsteroidal anti-inflammatory drugs.
Data presented as mean ± SD or numbers, with percentages in parentheses.
** Conditions/comorbidities: diabetes, thyroid disease, osteoporosis, stroke, hypertension, myocardial infarction, angina, congestive heart failure, chronic obstructive pulmonary disease, Parkinson disease, arthritis, and cancer.*

TABLE II. *Risk factors for history of prostatitis from multivariate logistic regression model**

Risk Factor	Odds Ratio (95% Confidence Interval)	*P* Value
Age (per 5-yr increase)	1.08 (1.02–1.15)	0.01
Race		
African American vs. white	0.88 (0.61–1.27)	0.50
Asian vs. white	0.65 (0.41–1.03)	0.07
Site		
Minneapolis vs. Birmingham	0.79 (0.62–1.00)	0.05
Palo Alto vs. Birmingham	0.62 (0.48–0.80)	0.0002
Pittsburgh vs. Birmingham	0.62 (0.49–0.78)	0.0001
Portland vs. Birmingham	0.89 (0.70–1.14)	0.36
San Diego vs. Birmingham	0.69 (0.54–0.87)	0.002
Health status		
Excellent/good vs. fair/poor/very poor	0.84 (0.69–1.02)	0.08
Comorbidity score† (per additional condition)	1.11 (1.04–1.18)	0.001
History of prostate cancer	5.40 (4.42–6.60)	<0.0001
History of benign prostatic hyperplasia	8.00 (6.76–9.47)	<0.0001
Prostate symptom score (per SD increase)	1.09 (1.01–1.18)	0.02
Dissatisfied with present urinary condition	1.24 (1.01–1.52)	0.04
Alcohol use	0.98 (0.84–1.13)	0.74
Finasteride use	1.89 (1.36–2.61)	0.0001
Alpha-blocker use	1.41 (1.18–1.67)	0.0001
Daily selenium intake (per SD increase)	1.05 (0.99–1.13)	0.12

** Using variables with P ≤0.10 in age and BPH-adjusted models.*
† Coded as 0, 1, 2, 3, 4+ conditions of 13 total medical conditions.

BPH, 9% for each standard deviation increase in the AUA Prostate Symptom Score, and 24% in men who reported being dissatisfied with their current urinary condition. We produced highly similar results when we ran forward, backward, and stepwise variable selection models (results not shown).

Significant differences were found between the effect of a couple of the baseline characteristics on a history of prostatitis for whites and African Americans (Table III). No significant interactions were noted for whites versus African Americans for any of the variables retained in the multivariate model. The only baseline characteristic in which the effect on prostatitis history was significantly different between whites and Asians was socioeconomic standing within the United States. Among white men, those with a history of prostatitis rated

TABLE III. *Comparison of baseline characteristics, prostate cancer history, and BPH history in men with and without a history of prostatitis*

Variable	Prostatitis History		*P* Value	Interaction *P* Value
	Yes	No		
Whites*	1352	4033		
Stroke	98 (7)	213 (5)	0.007	0.05†
Angina	236 (17)	540 (13)	0.0002	0.03†
Cancer	583 (43)	1046 (26)	<0.0001	0.03†
Caffeine intake (mg/day)	209.9 ± 231.5	223.5 ± 237.8	0.07	0.05†
Total calcium intake (mg/day)	1186.2 ± 574.3	1153.4 ± 595.0	0.08	0.04†
African Americans*	55	189		
Stroke	1 (2)	17 (9)	0.08	0.05†
Angina	18 (33)	26 (14)	0.001	0.03†
Cancer	25 (45)	29 (15)	<0.0001	0.03†
Caffeine intake (mg/day)	79.0 ± 128.6	142.0 ± 192.4	0.09	0.05†
Total calcium intake (mg/day)	946.1 ± 560.5	771.0 ± 433.0	0.04	0.04†
BPH				<0.0001
Yes	1199	1646		
Yes plus prostate cancer	265 (22)	116 (7)	<0.0001	
No	239	2736		
No plus prostate cancer	110 (46)	204 (7)	<0.0001	
Prostate cancer				<0.0001
Yes	375	320		
Yes plus BPH	265 (71)	116 (36)	<0.0001	
No	1063	4062		
No plus BPH	934 (88)	1530 (38)	<0.0001	

Key: BPH = benign prostatic hyperplasia.
Data presented as number of patients, with percentages in parentheses, unless otherwise noted.
* *Included only characteristics with significant interaction with race.*
† *Interaction* P *values repeat for characteristics under "Whites" and "African Americans" because interaction was between races, not those with and without history of prostatitis.*

their standing almost identically to those without a history of prostatitis (mean ± SD, 7.20 ± 1.72 versus 7.24 ± 1.67; $P = 0.41$). However, among Asian men, those with a history of prostatitis rated their standing significantly lower than did those without a history of prostatitis (5.53 ± 1.81 versus 6.56 ± 1.84; $P = 0.004$).

A significant interaction ($P < 0.0001$) was found between BPH and prostate cancer in the multivariate model, so we performed stratified analyses. Among men without a history of BPH (Table III), those with a history of prostatitis were more likely to report a history of prostate cancer compared with men without a history of prostatitis. The increase in the odds of a history of prostatitis for men with a history of prostate cancer was 8.8-fold (adjusted OR 8.8; 95% confidence interval [CI] 6.4 to 12.0). Among men with a history of BPH, those with a history of prostatitis were more likely to report a history of prostate cancer compared with men without a history of prostatitis. The increase in the odds of a history of prostatitis for men with a history of prostate cancer was 3.8-fold (adjusted OR 3.8; 95% CI 3.0 to 4.9).

Among men without a history of prostate cancer (Table III), those with a history of prostatitis were more likely to report a history of BPH than were men without a history of prostatitis. The increase was 9.8-fold in the odds of a history of prostatitis for men with a history of BPH (adjusted OR 9.8; 95% CI 8.0 to 12.0). Among men with a history of prostate cancer, those with a history of prostatitis were more likely to report a history of BPH than were men without a history of prostatitis, and the increase was 4.4-fold in the odds of a history of prostatitis for men with a history of BPH (adjusted OR 4.4; 95% CI 3.1 to 6.1).

COMMENT

A self-reported history of prostatitis is associated with self-reported prostate cancer and BPH and increased severity of LUTS and associated dissatisfaction. Because of the cross-sectional nature of the data, our findings do not suggest causality but do call for additional research into the relationship of prostatitis to other diseases of the prostate. The associations among these urologic conditions may reflect increased diagnostic surveillance for other prostatic diseases once one prostatic disease has been diagnosed, through mechanisms such as prostate-specific antigen measurement and urologic consultation. To the best of our knowledge, this is the first study to show an association be-

tween a history of prostatitis and current LUTS. A history of prostatitis in this cohort was associated with increased severity of LUTS and associated dissatisfaction with symptoms, even after controlling for a history of BPH. Men with a history of prostatitis had greater current mean AUA symptom scores and greater symptom dissatisfaction than did men without a history of prostatitis. The results of this study suggest that a history of prostatitis may play a role in LUTS and associated dissatisfaction, which may adversely affect patients' quality of life. These findings were more pronounced in African-American men, who reported the greatest mean AUA symptom scores and the most dissatisfaction with LUTS after controlling for age and a history of BPH. The associations between these urologic conditions require further study using more objective criteria.

Although prostate cancer is one of the most common cancers among men (particularly among African-American men), the etiology and much of the attributable risk remain unclear.[9] Although specific risk factors have not been well defined, several case-control and cohort studies, as well as two meta-analyses, have suggested a significant increase in the relative risk of prostate cancer in men with prostatitis and in those with a history of sexually transmitted disease.[1,2,10–13] A case-control study of prostate cancer among African Americans and whites revealed increased risks among men who reported a history of gonorrhea or syphilis or who had positive serology for syphilis.[14,15] Pooled relative risk estimates for prostate cancer and sexually transmitted diseases have shown a relative risk of 1.30 to 1.51 for prostate cancer, of 1.49 to 2.64 for syphilis, and 1.16 to 1.50 for gonorrhea.[16] The meta-analysis also found an association between prostate cancer and increased sexual activity. Furthermore, regular condom use has been shown to be protective against developing prostate cancer.[14] These findings suggest that sexually transmitted infectious agents may contribute to the etiology of prostate cancer. The general prevalence of chlamydia infections is 5% to 10%, although this range may be underestimated because many of these infections are asymptomatic in men.[17–19] Microbiologic organisms found in patients with prostatitis include *Chlamydia trachomatis, Ureaplasma, Mycoplasma, Neisseria gonorrhea, Pseudomonas, Escherichia coli,* and *Enterococcus* and various other gram-negative organisms.[20] Symptomatic and occult prostate infections may become chronic. It is biologically plausible that these chronic infections of the prostate may cause inflammation, hyperplasia, low-grade and high-grade dysplastic growth, and subsequent carcinogenesis. The current risk factors for prostate cancer, such as heredity, race, age, and dietary factors do not account for all the cases of prostate cancer. A chronic infection within the prostate may be important in the pathogenesis of prostate cancer by contributing to the inflammatory process and dysregulation of prostatic growth. A growing body of evidence is establishing infections of the prostate as a plausible and potentially modifiable risk factor for prostate cancer. Recent molecular studies have detected bacterial DNA sequences in prostatic tissue from patients with prostate cancer and chronic prostatitis.[21] Serologic studies have also found a greater prevalence of microbial antibodies in prostate cancer cases than in controls.[14] These data, as well as a compelling recent review of the mechanism of prostate cancer development, suggest chronic or recurrent inflammation may contribute to the pathogenesis of prostate cancer.[22] Prospective studies are clearly needed to test this hypothesis.

Our study had several important limitations. First, it was a cross-sectional study. The direction of the links between prostatitis and BPH and prostate cancer is unknown. However, it is well established that prostatitis occurs more commonly in younger men than in older men, and BPH and prostate cancer occur later in life and are more common in older men. Second, our study evaluated the history of prostate diagnoses only in older men, 65 years and older, and thus our findings may not be applicable to younger men. Third, our results may be subject to detection and recall bias over a lifetime, since a self-reported history of prostatitis was used in this study without further characterization of the diagnosis. Therefore, we could not exclude the possibility of misclassification of some of the prostatic diseases, because many symptoms of prostatitis are also similar to those of BPH. We could not determine whether some survey respondents were accurately or systematically underreporting or overreporting a history of prostatitis, although both prostatitis and BPH are underdiagnosed and hence would be expected to have been underreported by patients. We also could not further classify individuals' prostatitis as chronic versus acute, infectious versus noninfectious, or bacterial versus abacterial. A strength of the study was that the associations persisted after adjusting for a history of BPH, which is a likely confounder. Our study was not designed to assess the effect of prostatitis treatment and subsequent development of prostatic disease, so we were unable to determine whether treatment affects the incidence of BPH and prostate cancer. Another important strength of this study was that men in the MrOS cohort were not recruited with a primary focus on the investigation of prostate-related conditions or symptoms.

These results show that a history of prostatitis is common, that prostatitis is associated with pros-

tate cancer, and that it is associated with BPH and increased severity of current LUTS and associated dissatisfaction with current urinary condition. These data support the hypothesis that prostatitis may be a risk factor for the development of BPH and prostate cancer, because prostatitis is more common in younger men and usually precedes the development of these prostate conditions, which usually occur later as men age. We hypothesize that some cases of prostate cancer may be caused and/or facilitated by infections of the lower urologic tract. Several earlier studies have supported the hypothesis that prostate cancer has an infectious etiology.[1,2,10–15] The results of this study provide additional epidemiologic evidence of the possible relationship between prostatitis and prostate cancer and BPH. Such knowledge may have an effect on prostate cancer screening and the development of diagnostic tests for prostatitis, such as objective biomarkers and enhanced surveillance of persons at increased risk of developing prostate cancer, as well as on the assessment and treatment of persons with prostatitis.

CONCLUSIONS

Our study results have shown that a self-reported history of prostatitis is associated with self-reported prostate cancer and BPH and increased severity of LUTS and associated dissatisfaction. Understanding the associations between prostatitis and BPH and incident prostate cancer requires additional prospective studies to determine whether symptom-driven screening would be case finding and whether effective treatment of prostatitis would lead to a reduction in prostate cancer incidence, mortality, and preventive behaviors, and possibly lead to the primary prevention of BPH and prostate cancer.

REFERENCES

1. Roberts RO, Bergstralh EJ, Bass SE, *et al:* Prostatitis as a risk factor for prostate cancer. Epidemiology **15:** 93–99, 2004.
2. Dennis LK, Lynch CF, and Torner JC: Epidemiologic association between prostatitis and prostate cancer. Urology **60:** 78–83, 2002.
3. Roberts RO, Jacobson DJ, Girman CJ, *et al:* Prevalence of prostate-like symptoms in a community based cohort of older men. J Urol **168:** 2467–2471, 2002.
4. Collins MM, Meigs JB, Barry MJ, *et al:* Prevalence and correlates of prostatitis in the health professionals follow-up study cohort. J Urol **167:** 1363–1366, 2002.
5. Nickel JC, Downey J, Hunter D, *et al:* Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health Chronic Prostatitis Symptom Index. J Urol **165:** 842–845, 2001.
6. Kreiger JN, Riley DE, Cheah PY, *et al:* Epidemiology of prostatitis: new evidence for a world-wide problem. World J Urol **21:** 70–74, 2003.
7. Roberts RO, Lieber MM, Rhodes T, *et al:* Prevalence of a physician-assigned diagnosis of prostatitis: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. Urology **51:** 578–584, 1998.
8. Barry MJ, Fowler FJ Jr, O'Leary MP, *et al,* for the Measurement Committee of the American Urological Association: Correlation of the American Urological Association symptom index with self-administered versions of the Madsen-Iversen, Boyarsky and Maine Medical Assessment Program symptom indexes. J Urol **148:** 1558–1563, 1998.
9. Jemal A, Murray T, Samuels A, *et al:* Cancer statistics, 2003. CA Cancer J Clin **53:** 5–26, 2003.
10. Dennis LK, and Dawson DV: Meta-analysis of measures of sexual activity and prostate cancer. Epidemiology **13:** 72–79, 2002.
11. Mandel JS, and Schuman LM: Sexual factors and prostatic cancer: results from a case-control study. J Gerontol **42:** 259–264, 1987.
12. Pienta KJ, and Esper PS: Risk factors for prostate cancer. Ann Intern Med **118:** 793–803, 1993.
13. Key T: Risk factors for prostate cancer. Cancer Surv **23:** 63–77, 1995.
14. Hayes RB, Pottern LM, Strickler H, *et al:* Sexual behavior, STDs and risks for prostate cancer. Br J Cancer **82:** 718–725, 2000.
15. Rosenblatt KA, Wicklund KG, and Stanford JL: Sexual factors and the risk of prostate cancer. Am J Epidemiol **153:** 1151–1158, 2000.
16. Fowler JE Jr: Antimicrobial therapy for bacterial and nonbacterial prostatitis. Urology **60**(6 suppl):24–26, 2000.
17. LaMontagne DS, Fine DN, and Marrazzo JM: *Chlamydia trachomatis* infection in asymptomatic men. Am J Prev Med **24:** 36–42, 2003.
18. Farley TA, Cohen DA, and Elkins W: Asymptomatic sexually transmitted diseases: the case for screening. Prev Med **36:** 502–509, 2003.
19. Krieger JN, Ross SO, and Riley DE: Chronic prostatitis: epidemiology and role of infection. Urology **60**(6 suppl):8–12, 2002.
20. Weidner W, Schiefer HG, Krauss H, *et al:* Chronic prostatitis: a thorough search for etiologically involved microorganisms in 1,461 patients. Infection **19**(suppl 3):S119–S125, 1991.
21. Krieger JN, Riley DE, Vesella RL, *et al:* Bacterial DNA sequences in prostate tissue from patients with prostate cancer and chronic prostatitis. J Urol **164:** 1221–1228, 2000.
22. Nelson WG, De Marzo AM, and Isaacs WB: Prostate cancer. N Engl J Med **349:** 366–381, 2003.

Association between Past Urinary Tract Infections and Current Symptoms Suggestive of Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a major cause of illness, and its association with history of past urinary tract infections is unclear. We surveyed a racially, ethnically and socioeconomically diverse, community-based sample of adults aged 30–79 years in Boston, MA. This report gives estimates from the 2,301 men in the BACH survey: 700 black, 766 Hispanic and 835 white. Symptoms of chronic prostatitis—any perineal and/or ejaculatory pain and a pain score of ≥4—were derived from the NIH Chronic Prostatitis Symptom Index and were used to identify men with symptoms suggesting CP/CPPS. The overall prevalence of symptoms suggestive of CP/CPPS is 6.3%. The number of urinary tract infections, particularly >3, was associated with symptoms suggestive of CP/CPPS ($P<0.01$). There is a strong association between current symptoms of CP/CPPS and a history of urinary tract infections, particularly of multiple infections. The causality between chronic UTIs and CP/CPPS needs to be clarified by further study.

Key words: urinary tract infection ■ inflammation ■ prostate cancer

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INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common urologic problem that impairs quality of life in men and that is difficult to treat.[1–3] There is scant evidence about potential, particularly modifiable, risk factors for the development of chronic prostatitis symptoms.[4,5] Further identification and characterization of important risk factors could lead to the development of risk reduction strategies.

The National Institutes of Health (NIH) classifies prostatitis syndromes as acute bacterial, chronic bacterial, CP/CPPS and asymptomatic inflammatory prostatitis.[6] The most common is CP/CPPS, which is characterized by persistent discomfort or pain in the pelvic area and/or ejaculatory pain. The cause of CP/CPPS is unknown; few studies have explored its risk factors, and treatment with antimicrobial agents and alpha-blockers has not shown significant improvement in symptoms or quality of life.[7,8] This study was funded by NIH due to a recommendation by an NIH consensus panel that research on urologic conditions in minorities be given the highest priority. Despite that minorities are thought to be at elevated risk for many of these disorders, research has tended to focus on older, white populations.

The objective of this report is to describe the prevalence of CP/CPPS; the distribution by race/ethnicity, age and socioeconomic status (SES); and the association of current symptoms of CP/CPPS with a history of urinary tract infections (UTIs) in a community-based, random sample of men.

METHODS

The Boston Area Community Health (BACH) survey is designed to estimate the prevalence of symptoms of urological disorders in a multiethnic, community-based sample of adults aged 30–79 years. Using a stratified cluster sample, 5,506 adult men and women were recruited in three racial/ethnic groups: Hispanic,

black and white. This is a random sample of community-dwelling men and women, not a sample of patients. This report is based on the 2,301 men included in the BACH study: 700 blacks, 766 Hispanics and 835 whites.

Overall Design

The BACH study is a population-based, random-sample, epidemiologic survey of a broad range of urologic and urogynecologic symptoms that is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of NIH. The research design called for equal numbers of subjects in each of 24 design cells defined by age (30–39, 40–49, 50–59 and 60–79 years), sex and race/ethnicity (black, Hispanic and white). The BACH two-stage, stratified cluster sample (n=5,506) was recruited from April 2002 through June 2005.

Stratified, Two-Stage Cluster Sample

For the study, the city of Boston was divided into four geographic areas and three levels of minority density (a total of 12 strata). The levels of minority density were low-density minority (primarily white), high-density black (≥25% of the residents were black) and high-density Hispanic (≥30% of the residents were Hispanic). Census blocks were randomly sampled from 4,266 blocks in the city of Boston by stratum such that approximately 10% of the low-density minority blocks, 15% of the high-density black blocks, and 75% of the high-density Hispanic blocks were selected.

Sampling proceeded in five batches, each a random subsample (or "mini-version") of the overall BACH study.[9] Households from selected census blocks were identified using a current Boston Resident List that had been geocoded (Caliper, Newton, MA) with census tract and block information for each individual. Telephone numbers were obtained from a telephone matching service (Telematch Gannett, Springfield, VA) for approximately half of the selected individuals. One individual per household was designated as the primary contact person, with preference given to a person with a telephone number. Introductory letters were mailed to the selected households requesting a contact telephone number, if not already available (47.5% of the households). Households were screened either by telephone or by a field visit (if screeners were unable to reach the household by telephone). Screening was completed for 36% of the selected households, 30% of the households refused screening, and 34% of the households could not be contacted after 10 telephone calls, three mailings and three field visits (16 attempts to reach them).

Individuals from the selected census blocks were chosen according to eligibility rules to achieve our goal

Table 1. Symptoms suggestive of chronic prostatitis/chronic pelvic pain syndrome by characteristics of the 2,301 men in the BACH study—weighted to the population of Boston

Characteristics	Men			Black Men			Hispanic Men			White Men		
	%	SE	P Value[1]	%	SE	P Value[1]	%	SE	P Value[1]	%	SE	P Value[1]
Race/Ethnicity			0.8902									
Black	6.4	1.1										
Hispanic	5.7	1.3										
White	6.4	1.3										
Age Group (Years)			0.1170			0.0301			0.5151			0.3993
30–39	4.0	1.5		2.0	1.4		4.2	1.7		4.6	2.2	
40–49	5.3	1.3		7.0	2.2		5.3	2.6		4.5	1.9	
50–59	8.1	1.8		9.0	3.1		9.3	3.8		7.4	2.5	
60–79	10.6	2.5		10.9	3.3		8.4	3.4		10.7	3.4	
Socioeconomic Status			0.5925			0.2366			0.7919			0.7762
Lower	7.7	1.5		8.2	2.2		6.1	1.6		8.8	3.8	
Middle	6.1	1.1		5.8	1.7		5.8	2.5		6.3	1.5	
Upper	5.4	2.0		2.7	2.4		3.4	3.4		5.8	2.3	
History of PC			0.0437			0.0563			0.8928			0.2883
Yes	20.9	7.5		36.2	13.9		6.6	7.0		15.7	9.0	
No	6.0	0.9		5.7	1.1		5.7	1.3		6.2	1.3	
History of UTI			0.0519			0.2845			0.3040			0.1062
Yes	12.9	3.5		12.6	5.7		12.7	7.1		13.0	5.7	
No	5.6	0.8		5.8	1.2		5.2	1.2		5.7	1.2	
Smoking Status			0.3833			0.4713			0.8737			0.3806
Never	5.0	1.1		5.6	1.7		6.4	2.3		4.3	1.6	
Former	7.2	1.9		4.7	2.1		5.0	1.8		8.2	2.7	
Current	7.1	1.4		8.1	2.1		5.1	1.5		7.0	2.2	

BACH: Boston Area Community Health; UTI: urinary tract infection; PC: prostate cancer; SE: standard error; 1: P value from a Chi-squared test. The null hypothesis is that the prevalence of symptoms suggestive of chronic prostatitis/chronic pelvic pain syndrome is the same across the levels of the variable considered.

of approximately equal numbers of black, white and Hispanic respondents by sex in four age categories: 30–39, 40–49, 50–59 and 60–79 years. Some of the eligibility rules used in BACH were any age-eligible subject and any age-eligible black or Hispanic male subject. Eligibility rules varied by batch and were randomly assigned to selected households based on household demographics at the start of each batch. BACH inclusion criteria included self-identified as black, white or Hispanic race/ethnicity, aged 30–79 years, competent to sign informed consent, and able to speak English or Spanish well enough to complete the survey. In total, we recruited 5,506 people: 2,301 men and 3,205 women consisting of 1,770 blacks, 1,877 Hispanics and 1,859 whites. Interviews were completed with 63.3% of the screener-identified eligible individuals from the selected households. Of the 5,506 interviews, 1,461 (26.5%) were conducted in Spanish, mostly with Hispanic subjects.

Because of design requirements, the BACH subjects had unequal probabilities of selection into the study. For analyses to be representative of the city of Boston, it was necessary to weight observations inversely proportional to their probability of selection into the study.[10,11] Weights were further poststratified to the population of Boston according to the 2000 Census. Demographics and basic health-related variables were compared between BACH and the Boston sample of the Behavioral Risk Factor Surveillance System (BRFSS), and results were found to be comparable. Basic health-related variables were compared between BACH and national government surveys [National Health Interview Survey: www.cdc.gov/nchs/nhis.htm; National Health and Nutrition Examination Survey (NHANES): www.cdc.gov/nchs/nhanes.htm; and BRFSS: www.cdc.gov/brfss/], and the results were found to be comparable, indicating that the results from BACH may be generalizable to the United States as a whole.

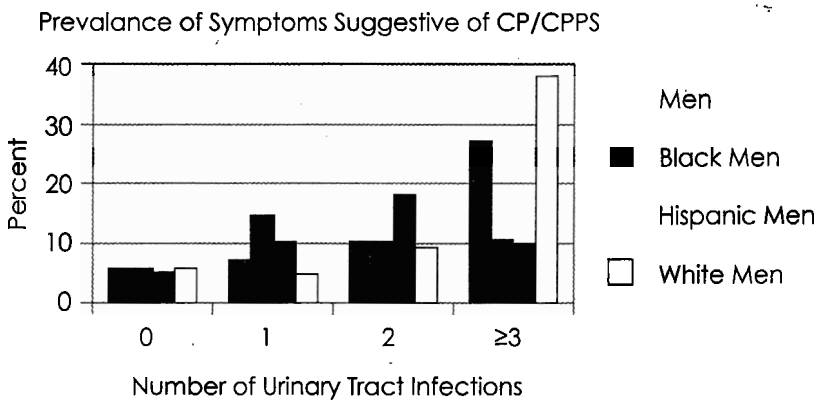
DATA COLLECTION

Data were obtained during a two-hour, in-person interview, generally conducted in the subject's home by a well-trained (bilingual) interviewer.[12] Following written informed consent [all protocols and informed consent procedures were approved by New England Research Institutes (NERI) institutional review board], anthropometric measurements (blood pressure, height and weight) were obtained, along with information on medical (sexually transmitted diseases, kidney infections, vasectomy, alcohol use and smoking habits) and reproductive history, major comorbidities, prescription and over-the-counter medications, lifestyles, psychosocial factors, medical care utilization, and detailed self-reported major symptoms of seven different urogynecologic conditions (urinary incontinence, benign prostatic hyperplasia, interstitial cystitis/chronic pelvic pain, prostatitis, hypogonadism/androgen deficiency, erectile dysfunction, female sexual dysfunction). Wherever possible, the questions and scales employed on BACH were selected from published instruments with documented metric properties and, following some minor modifications, were approved by a scientific advisory committee of experts in urology and urogynecology. To ensure acquisition of the highest-quality data, all staff were trained, certified, monitored and regularly retrained in all procedures and protocols. A minimum of 10% double data entry helped ensure accurate data computerization. Regular reports from ADEPT, NERI's electronic data capture software (NERI, Watertown, MA), closely monitored all aspects of data completeness and quality.

Variables of Interest

The BACH survey includes modified NIH Chronic Prostatitis Symptom Index (NIH-CPSI)[13] questions that pertain to urogenital pain and urinary symptoms during a time frame of one month. The longer time frame from the standard one-week period may increase the prevalence

Figure 1. Prevalence of symptoms suggestive of chronic prostatitis/chronic pelvic pain syndrome by number of urinary tract infections in the 2,301 men from the BACH survey



of these symptoms. Any perineal and/or ejaculatory pain and a CPSI pain score of ≥4 were used to identify men who had symptoms suggesting prostatitis.[14,15] Although prostatitis is a clinical diagnosis of exclusion, this definition has been found to be useful in epidemiological studies.[14,15] Socioeconomic status (SES) was determined using a combination of education and income[16] and categorized such that 25% of the population was of lower, 50% of middle and 25% of upper socioeconomic status. Quality of life was measured by the SF-12 instrument and converted to physical and mental health component scores.[17] In the baseline questionnaire, participants were asked: "Have you ever been told by your healthcare provider that you had a bladder infection (urinary tract infection or cystitis) or kidney infection (pyelonephritis)?" If they answered "yes," they were also asked: "How many times were you diagnosed with a bladder infection (urinary tract infections or cystitis) in your lifetime?"

Statistical Analyses

Multiple imputation (MI) was used to impute missing values using the procedure in SAS® version 9.1 (SAS Institute Inc., Cary, NC).[18-20] Statistical analyses, taking into account the two-stage cluster survey design using sampling weights, were performed using SUDAAN® version 9.0.1 (Research Triangle Institute, Research Triangle Park, NC).[21] The strength of the association of symptoms suggestive of CP/CPPS and categorical variables was measured by a Chi-squared statistic. Analysis of variance was used to measure the association of symptoms of prostatitis and continuous variables. A multiple logistic regression model was used to model the overall association of symptoms of CP/CPPS and multiple covariates, and was used to calculate the odds ratios and 95% confidence intervals.

Covariates (Table 1) were entered as categorical variables with the exception of SES, which was entered as a continuous variable. Keeping age group and race/ethnicity in the model, covariates were removed using backwards elimination. Covariates were kept in the model if $P<0.05$ overall or for ≥1 racial/ethnic group.

RESULTS

Demographic and some health characteristics for the BACH sample are reported in Table 2. The overall prev-

Table 2. Characteristics of the 2,301 men in the BACH survey—weighted to the population of Boston

Characteristics	Men	Black Men	Hispanic Men	White Men	P Value[1]
Born in United States	77.5	75.5	15.9	91.2	<0.0001
Years of Education (≤12)	33.0	45.9	66.1	20.8	<0.0001
Socioeconomic Status					<0.0001
Lower	24.0	36.9	58.4	11.6	
Middle	49.2	53.2	30.4	51.5	
Upper	26.8	9.9	11.2	36.8	
Marital Status (married or living with a partner)	55.3	47.2	64.3	56.6	0.0002
Health Insurance					<0.0001
Private	67.4	56.7	43.2	76.8	
Public (Medicare, Medicaid) only	19.9	27.2	26.2	12.5	
None	14.7	16.1	30.7	10.7	
Smoking Status					0.0003
Never	38.8	40.4	48.9	36.1	
Former	28.9	22.3	25.0	32.4	
Current	32.3	37.3	26.0	31.5	
Body Mass Index					0.0437
<25	26.5	27.4	26.4	26.2	
25–30	40.8	33.8	42.0	43.4	
≥30	32.7	38.8	31.6	30.4	
General Health Status					<0.0001
Excellent	20.0	15.6	15.0	22.9	
Very good	33.6	29.4	21.4	37.8	
Good	31.5	36.6	33.6	29.0	
Fair	11.7	14.7	27.1	7.2	
Poor	3.3	3.8	2.9	3.1	
Number of Urinary Tract Infections					0.2512
0	91.0	92.0	93.7	90.1	
1	4.6	4.1	2.8	5.2	
2	2.2	1.3	2.0	2.5	
3+	2.2	2.7	1.5	2.2	
Prostate Cancer	1.8	2.1	1.0	1.9	0.3804

BACH: Boston Area Community Health; 1: P value from a Chi-squared test. The null hypothesis is that the distribution of the variable is the same across the three race/ethnic groups.

alence of symptoms suggestive of CP/CPPS was 6.3%. Table 1 gives bivariate associations of symptoms suggestive of CP/CPPS with categorical variables and Table 3 with continuous variables. In bivariate analyses, symptoms suggestive of chronic prostatitis increased with age, did not differ by race/ethnicity and increased with lower SES (although this was not statistically significant). Twenty-one percent of respondents with a history of prostate cancer had symptoms of chronic prostatitis, compared with only 6% of those without a history of prostate cancer (P=0.04). Of men with a history of a sexually transmitted disease, 7.6% had symptoms of chronic prostatitis, compared with 6% of those without a history of a sexually transmitted disease (P=0.38) (data not shown). Symptoms of CP/CPPS were seen in 5.7% of respondents without a history of UTIs, compared with 7.3% of those with one UTI, 10.3% of those with two and 27.2% of those with ≥3 (P=0.19) (Figure 1). Persons with symptoms of chronic prostatitis had significantly lower physical and mental health component scores and significantly greater numbers of healthcare provider visits in the past year.

In a multiple logistic regression model (Table 4), the number of UTIs in a patient's history was associated with symptoms suggestive of CP/CPPS (P=0.0075). Men with ≥3 UTIs had almost five-fold higher odds of having symptoms suggestive of chronic prostatitis/chronic pelvic pain, compared with men without a history of multiple UTIs. An overall trend was noted between a history of prostate cancer and CP/CPPS (P=0.09) after adjusting for age, race/ethnicity and number of UTIs. The association between UTIs and chronic prostatitis symptoms was stronger for whites (P=0.003) than for blacks or Hispanics, while the association between prostate cancer and symptoms suggestive of CP/CPPS was stronger for blacks (P=0.03) than for whites or Hispanics.

DISCUSSION

This study[1] from the BACH survey—one of few racially and ethnically diverse community-based U.S. samples to examine a broad range of urological symptoms suggestive of different urologic diseases—found a strong association between current symptoms suggestive of CP/CPPS and a self-reported history of UTIs, particularly for whites. This association is biologically plausible because the mechanisms of bacterial prostatitis (acute and chronic) are believed to include ascension of urethral microbes or reflux of urine from the bladder into the prostate, with subsequent infection and/or inflammation of the prostate.[22] The mechanism or role of infection in CP/CPPS (category-3) patients in our study, however, is unclear. To our knowledge, this study may be the first to demonstrate a clear association between an increasing number of past UTIs and symptoms suggestive of current CP/CPPS. An odds ratio of 4 (for ≥3 UTIs) is unlikely to occur by chance. A recently published case-control study examining risk factors for CP/CPPS also found that men with the syndrome were significantly more likely to have a history of UTIs.[23]

Prior studies have shown that the risk of UTIs in men is increased by lack of circumcision, as well as unprotected sexual intercourse, benign prostatic hyperplasia, renal stones, increasing age and urethral instrumentation.[24-29] In contrast to women, very little is known about UTIs in men,[30,31] partly due to low incidence.[32] In our population from the BACH survey, 9.0% of men had a history of ≥1 UTI. Current research on UTIs in men shows that men and women have similar infecting bacte-

Table 3. Association of continuous variables and symptoms suggestive of chronic prostatitis/chronic pelvic pain syndrome in the 2,301 men from the BACH survey—weighted to the population of Boston

	Men			Black Men			Hispanic Men			White Men		
Symptoms Suggestive of CP/CPPS	**Yes**	**No**	**P Value[1]**	**Yes**	**No**	**P Value[1]**	**Yes**	**No**	**P Value[1]**	**Yes**	**No**	**P Value[1]**
Continuous Variables												
Age (Years)			0.0192			0.0014			0.1112			0.1631
Mean	52.3	47.3		54.3	47.3		47.8	44.0		52.3	48.0	
Standard error	2.0	0.5		2.1	0.7		2.3	0.5		2.9	0.7	
Physical HCS			<0.0001			<0.0001			0.0012			0.0065
Mean	43.7	50.7		39.8	1.8		42.5	50.5		45.5	51.3	
Standard error	1.5	0.3		49.4	0.6		2.3	0.5		2.1	0.4	
Mental HCS			0.0002			0.0063			0.0029			0.0130
Mean	44.7	50.8		44.1	2.2		43.5	51.2		45.2	50.8	
Standard error	1.5	0.4		50.3	0.6		2.4	0.5		2.2	0.5	
Number of Visits to HCP in Past Year			0.0003			0.0337			0.0522			0.0101
Mean	14.4	7.4		12.2	6.8		9.8	4.7		16.1	8.3	
Standard error	1.9	0.5		2.4	0.7		2.6	0.4		2.9	0.7	

BACH: Boston Area Community Health; CP/CPPS: chronic prostatitis/chronic pelvic pain syndrome; HCS: health component score; HCP: healthcare provider; 1: P value from analysis of variance. The null hypothesis is that the mean value of the variable considered is the same for men with and without symptoms suggestive of CP/CPPS.

rial species, host predispositions and treatment results.[33] One important and obvious difference is the presence of a prostate gland in men and poor antimicrobial penetrance into this gland. Total annual healthcare expenditures are slightly higher for men than for women with UTIs ($5,544 vs. $5,407 per year), and mean time lost from work due to cystitis is also higher for men (10.5 vs. 4.8 hours).[34]

The NIH-CPSI, a validated symptom index, is used in men with symptoms suggestive of CP/CPPS to quantify symptoms and response to treatment. The questionnaire has been proven to have a high degree of internal consistency and reliability when self-administrated in clinical practice for patients with chronic prostatitis.[35] The NIH-CPSI total score has been accepted as a reliable outcome measure for prostatitis treatment in primary and secondary care patients with varying duration of prostatitis-like symptoms, and supplementation with measures of pain intensity and activity may improve its usefulness.[35] We used any perineal and/or ejaculatory pain and a pain score of ≥4, as previously done in the medical literature, to identify men with symptoms suggesting CP/CPPS and to distinguish them from normal controls and men with benign prostatic hyperplasia.[14,15] It is important to note that our study may overestimate the prevalence or symptoms suggestive of CP/CPPS because we used a modified NIH-CPSI tool by altering the order of symptom query in our survey instrument and by using a one-month period instead of one-week period (as used by Roberts et al.), which may have allowed us to identify more men with chronic prostatitis-like symptoms. However, in our study, the overall prevalence of symptoms suggestive of CP/CPPS was 6.3%, which is within the range of overall prevalence of prostatitis previously estimated at between 2–16%.[2,14,15,36-39]

History of prostate cancer also had an overall association with symptoms suggestive of chronic prostatitis in our multivariate model (statistically significant only for blacks), although it is unknown whether the onset of CP/CPPS symptoms preceded the cancer diagnosis. It is unclear how the higher incidence of prostate cancer among blacks affects symptoms suggestive of CP/CPPS. The lack of overall significance may be related to the small number of persons with a history of prostate cancer (n=50). Associations between prostate cancer and chronic prostatitis have been reported, but the exact relation has not been well characterized. It is clear that lower urinary tract symptoms or symptoms of prostatitis may prompt prostate-specific antigen testing and digital rectal examination, which increase the likelihood of a prostate cancer diagnosis. On the other hand, data increasingly suggest that inflammation of the prostate may promote carcinogenesis, similar to the association of inflammation with other cancers.[40–42] Current symptoms of CP/CPPS were associated with an increased number of healthcare provider visits in the past year and with decreasing physical and mental health component scores. These findings suggest that persons with more severe symptoms suggestive of CP/CPPS tend to see providers more often and to have lower physical and mental health scores, possibly due to their age and/or comorbid problems that increase the likelihood of social isolation and reduce physical activity or because CP/CPPS symptoms decrease overall quality of life.

Our study has several limitations. Because of the cross-sectional nature of the data, our findings do not

Table 4. Results from a logistic regression model for symptoms suggestive of chronic prostatitis/chronic pelvic pain syndrome in the 2,301 men from the BACH survey

Characteristic	Men			Black Men			Hispanic Men			White Men		
	OR	95% CI	P Val[1]	OR	95% CI	P Val[1]	OR	95% CI	P Val[1]	OR	95% CI	P Val[1]
Race/Ethnicity			0.9777									
Black	1.00	0.56, 1.78										
Hispanic	1.06	0.59, 1.89										
White	1.00	reference										
Age Group (Years)			0.2585			0.4670			0.5719			0.4991
30–39	1.00	reference		1.00	reference		1.00	reference		1.00	reference	
40–49	1.29	0.50, 3.32		3.75	0.64, 22.15		1.20	0.33, 4.31		0.85	0.23, 3.20	
50–59	1.93	0.75, 4.96		4.65	0.68, 31.79		2.44	0.65, 9.15		1.34	0.37, 4.82	
60–79	2.36	0.86, 6.49		4.97	0.63, 31.79		1.85	0.50, 6.79		1.98	0.55, 7.06	
History of UTIs			0.0075			0.7986			0.5056			0.0034
0	1.00	reference		1.00	reference		1.00	reference		1.00	reference	
1	1.30	0.50, 3.39		2.07	0.40, 10.78		1.92	0.37, 9.99		0.82	0.18, 3.64	
2	**1.50**	**0.48, 4.63**		**0.55**	**0.04, 10.78**		**3.79**	**0.57, 25.06**		**1.45**	**0.30, 6.92**	
3+	4.91	1.95, 12.40		1.36	0.15, 12.37		2.04	0.19, 21.94		8.34	2.69, 25.90	
History of PC	2.41	0.87, 6.64	0.0897	7.37	1.24, 43.91	0.0327	1.03	0.12, 8.55	0.9758	1.33	0.29, 6.04	0.7145

BACH: Boston Area Community Health; UTI: urinary tract infection; PC: prostate cancer; 1: P value from logistic regression. The null hypothesis is that the variable does not have an effect on the likelihood that a man has symptoms suggestive of chronic prostatitis/chronic pelvic pain syndrome.

suggest causality but call for additional research into the relation of a history of UTIs and current CP/CPPS symptoms. There are plans for BACH to evolve into a prospective cohort study. Moreover, it is possible that misclassification may have occurred if physicians labeled early symptoms suggestive of CP/CPPS as UTIs. The reliability of self-report (e.g., questionnaires) of chronic prostatitis symptoms and UTIs is largely unknown in a community-based population. Because CP/CPPS in particular is often a clinical diagnosis of exclusion and therefore is difficult to definitively diagnose, respondents may have reported an incorrect diagnosis of UTI. Alternatively, the strengths of the study lie in the large sample size of different racial, ethnic and socioeconomic groups; the random selection of study participants from the general community; and the emphasis on urological symptoms rather on than diagnosed diseases.

In conclusion, these results show that an increasing number of past UTIs is positively associated with symptoms suggestive of CP/CPPS. Reduction of recurrent UTIs may decrease the development of CP/CPPS symptoms, which are difficult to treat. Clinicians might consider ordering a urine culture and consider the diagnosis of UTI when men present with urethritis. Our study was not designed to demonstrate modification of risk factors for symptoms of CP/CPPS. Nevertheless, it is prudent to recommend that patients take precautions, such as using protective barriers during sexual intercourse and seeking care for symptoms of bladder obstruction, to reduce exposure to microbes that can cause UTIs. Further study is needed to determine if prevention of recurrent UTIs can reduce the risk of CP/CPPS symptoms and to clarify causality between chronic UTIs and CP/CPPS.

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REFERENCES

1. Collins MM, Stafford RS, O'Leary MP, et al. How common is prostatitis? A national survey of physician visits. *J Urol.* 1998;159(4):1224-1228.

2. Roberts RO, Lieber MM, Rhodes T, et al. Prevalence of a physician-assigned diagnosis of prostatitis: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. *Urology.* 1998;51:578-584.

3. Turner JA, Hauge S, Von Korff M, et al. Primary care and urology patients with the male pelvic pain syndrome: symptoms and quality of life. *J Urol.* 2002;167:1768-1773.

4. Berger RE, Krieger JN, Kessler D, et al. Case-control study of men with suspected idiopathic prostatitis. *J Urol.* 1989;141:328-331.

5. Rothman I, Stanford JL, Kuniyuki A, et al. Self-report of prostatitis and its risk factors in a random sample of middle-aged men. *Urology.* 2004;64:876-879.

6. Nickel JC, Nyberg LM, Hennenfent M. Research guidelines for chronic prostatitis: consensus report from the first National Institutes of Health International Prostatitis Collaborative Network. *Urology.* 1999;54:229-233.

7. Wagenlehner FM, Naber KG. Fluoroquinolone antimicrobial agents in the treatment of prostatitis and recurrent urinary tract infections in men. *Curr Infect Dis Rep.* 2005;7:9-16.

8. Weidner W. Treating chronic prostatitis: antibiotics no, alpha-blockers maybe. *Ann Intern Med.* 2004;141:639-640.

9. Feldman HA, McKinlay SM, Niknian M. Batch sampling to improve power in a community trial. Experience from the Pawtucket Heart Health Program. *Evaluation Review.* 1996;20(3):244-274.

10. Cochran WG. Sampling Techniques, 3rd ed. New York, NY: John Wiley & Sons; 1977.

11. Kish L. Survey Sampling. New York, NY: John Wiley & Sons; 1965.

12. McKinlay SM, Kipp DM, Johnson P, et al. "A field approach for obtaining physiological measures in surveys of general populations: Response rates, reliability, and costs." In: *Health Survey Research Methods: Proceedings of the fourth conference on Health Survey Research Methods,* Washington, DC; 1982:195-204. DHHS Pub. No. (PHS) 84-3346 (September 1984).

13. Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al and the Chronic Prostatitis Collaborative Research Network. The National Institutes of Health Chronic Prostatitis Symptom Index: Development and Validation of a New Outcome Measure. *J Urology.* 1999;162(2):369-375.

14. Nickel JC, Downey Hunter D, et al. Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health Chronic Prostatitis Symptom Index. *J Urology.* 2001;165: 842-845.

15. Roberts RO, Jacobson DJ, Girman CJ, et al. Prevalence of prostate-like symptoms in a community based cohort of older men. *J Urology.* 2002;168: 2467-2471.

16. Green LW. Manual for Scoring Socioeconomic Status for Research on Health Behavior. *Public Health Rep.* 1970;85(9):815-827.

17. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996;34(3):220-233.

18. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley and Sons Inc.; 1987.

19. Schafer JL. Analysis of Incomplete Multivariate Data. New York, NY: Chapman and Hall; 1997.

20. SAS/STAT User's Guide. Cary, NC: SAS Institute Inc.; 2003.

21. Research Triangle Institute. SUDAAN Language Manual Release 9.0, Research Triangle Park, NC: Research Triangle Institute; 2004.

22. Lipsky BA. Prostatitis and urinary tract infection in men: what's new; what's true? *Am J Med.* 1999;106:327-334.

23. Pontari MA, McNaughton-Collins M, O'Leary MP, et al. The CPCRN Study Group. A case-control study of risk factors in men with chronic pelvic pain syndrome. *BJU Int.* 2005;96(4):559-565.

24. Spach DH, Stapleton AE, Stamm WE. Lack of circumcision increases the risk of urinary tract infection in young men. *JAMA.* 1992;267:679-681.

25. Winberg J. The prepuce: a mistake of nature? *Lancet.* 1989;1(8638):598-599.

26. Barnes RC, Daifuku R, Roddy RE, et al. Urinary tract infections in sexually active homosexual men. *Lancet.* 1986;1:171-173.

27. Chinn RH, Maskell R, Mead JA, et al. Renal stones and urinary infection: A study of antibiotic treatment. *BMJ.* 1976;2:1411.

28. Boscia JA, Kobasa WD, Knight RA, et al. Epidemiology of bacteriuria in an elderly ambulatory population. *N Engl J Med.* 1986;309:1420-1425.

29. Nicolle LE, Henderson E, Bjornson J, et al. The association of bacteriuria with resident characteristics in elderly institutionalized men. *Ann Intern Med.* 1987;106:682-686.

30. Schaeffer AJ. Urinary tract infection in men—state of the art. *Infection* 1994;22(suppl 1):S19-S21.

31. Pewitt EB, Schaeffer AJ. Urinary tract infection in urology, including acute and chronic prostatitis. *Infect Dis Clin North Am.* 1997;11(3):623-646.

32. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Dis Mon.* 2003;49(2):53-70.

33. Ulleryd P. Febrile urinary tract infection in men. *Int J Antimicrob Agents.* 2003;22(suppl 2):89-93.

34. Griebling TL. Urologic diseases in america project: trends in resource use for urinary tract infections in men. *J Urol.* 2005;173(4):1288-1294.

35. Turner JA, Ciol MA, Von Korff M, et al. Validity and responsiveness of the national institutes of health chronic prostatitis symptom index. *J Urol.* 2003;169(2):580-583.

36. Nickel JC, Elhilali M, Vallancien G, ALF-ONE Study Group. Benign prostatic hyperplasia (BPH) and prostatitis: prevalence of painful ejaculation in

men with clinical BPH. *BJU Int.* 2005;95:571-574.

37. Collins MM, Meigs JB, Barry MJ, et al. Prevalence and correlates of prostatitis in the health professionals follow-up study cohort. *J Urology.* 2002;167:1363-1366.

38. Kreiger JN, Riley DE, Cheah PY, et al. Epidemiology of prostatitis: new evidence for a world-wide problem. *World J Urol.* 2003;21:70-74.

39. Roberts RO, Lieber MM, Rhodes T, et al. Prevalence of a physician-assigned diagnosis of prostatitis: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. *Urology.* 1998;51:578-584.

40. Nelson WG, De Marzo AM, DeWeese TL, et al. The role of inflammation in the pathogenesis of prostate cancer. *Urology.* 2004;172:S6-S11.

41. Platz EA, De Marzo AM. Epidemiology of inflammation and prostate cancer. *J Urol.* 2004;171(2 Pt 2):S36-S40.

42. Palapattu GS, Sutcliffe S, Bastian PJ, et al. Prostate carcinogenesis and inflammation: emerging insights. *Carcinogenesis.* 2004;26(7):1170-1181. ■

SUPPORTING DATA

TABLE 1. Characteristics of VA Men Cases and Controls

	Cases (n=65)	Controls (n=195)	*p* value †
Current age			
≤ 55	2 (3.08%)	6 (3.08%)	
55-65	7 (10.77)	21 (10.77)	
65-75	17 (26.15)	51 (26.15)	0.98
75-85	27 (41.54)	81 (41.54)	
85-95	11 (16.92)	33 (16.92)	
> 95	1 (1.54)	3 (1.54)	
Race			
Asian or pacific islander	3 (4.62)	9 (4.62)	
Black	17 (26.15)	51 (26.15)	
Latino or hispanic	2 (3.08)	6 (3.08)	1
White	28 (43.08)	84 (43.08)	
Unknown	15 (23.08)	45 (23.08)	
Number of visits			
≤ 50	7 (10.77)	44 (22.56)	
50-100	18 (27.69)	63 (32.31)	0.01
100-150	20 (30.77)	48 (24.62)	
> 150	20 (30.77)	40 (20.51)	
Years of enrollment			
≤ 10	12 (18.46)	23 (11.79)	
10-15	16 (24.62)	55 (28.21)	0.25
15-20	11 (16.92)	46 (23.59)	
> 20	26 (40.00)	71 (36.41)	
History of prostatitis	1 (1.54)	8 (4.10)	0.46
History of BPH	41 (63.08)	114 (58.46)	0.56
Elevated PSA (>4.0)	21 (32.31)	27 (13.85)	<0.05
History of UTI	57 (87.69)	151 (77.44)	0.08

† The comparisons for current age, number of visits, and year of enrollment use the Wilcoxon rank sum test; all other comparisons use Fisher's exact test

Table 2: Antibiotic and Anti-Inflammatory Use and Prostate Cancer Risk: Results from a Logistic Regression Model

No. antibiotic prescriptions	OR (95% CI)	Trend *P-value*
0	Reference	0.33
1-25	1.31 (0.50,3.40)	
26-50	0.60 (0.20,1.82)	
51-100	0.62 (0.22,1.76)	
101^{+}	0.78 (0.30,1.98)	

No. anti-inflammatory prescriptions	OR (95% CI)	Trend *P-value*
0	Reference	0.25
1-500	0.88 (0.41,1.91)	
501-1000	0.28 (0.07,1.15)	
1001-1500	0.62 (0.20,1.90)	
1501^{+}	0.62 (0.24,1.59)	

No. aspirin prescriptions	OR (95% CI)	Trend *P-value*
0	Reference	0.35
1-500	0.60 (0.26,1.38)	
501-1000	0.43 (0.13,1.42)	
1001-1500	0.40 (0.12,1.38)	
1501^{+}	1.04 (0.36,3.00)	

*ORs adjusted for age group, race, years of enrollment, and number of visits